ELRIAH-PC | Medical Journal of Viral Hepatitis

Original Article

Frequency and characterization of mixed ascites among cirrhotic patients admitted to Zagazig University hospital

Ibrahim Ibrahim[1*], Elsaid Elbadrawy[1], Dina Nasr[1], Hanaa El-Said[2], Sameh Abdel Monem[1].

[1]*Tropical Medicine dept., Faculty of Medicine, Zagazig Univ., Zagazig, Egypt;*
[2]*Clinical Pathology dept., Faculty of Medicine, Zagazig Univ., Zagazig, Egypt.*
*ibrahimibrahim1979@yahoo.com

Received: 22-12-2019 **Accepted:** 5-3-2020

Abstract: *Background and aim.* Mixed ascites is defined in patients in whom two or more etiologies of ascites are demonstrated. Such patients have liver cirrhosis plus (an) other local and/or systemic cause(s). The aim of this work is to detect the frequency and characterization of mixed ascites among cirrhotic patients. *Patients and methods.* The study was conducted on 273 ascitic cirrhotic patients. All patients were subjected to full history taking, thorough clinical examination, radiological investigations and laboratory investigations including CRP and tumor markers (AFP, CEA, CA 19-9, CA 125). Diagnostic abdominal paracentesis with cytologic and biochemical analyses and Ziehl- Neelsen staining of ascitic fluid were done. Also, serum-ascites albumin gradient (SAAG) was calculated. *Results.* Twenty eight patients (10.3%) among the studied patients were mixed ascites. Among patients with mixed ascites, the most common cause was malignancy in 11 patients (39.2%), cardiac causes were present in 7 patients (25%), renal causes were found in 2 patients (7.1%) and surgical abdominal causes were present in 8 patients (28.7%). Compared to non-mixed ascites, patients with mixed ascites had a statistically significant increase regarding ascitic total leucocytic count, lactate dehydrogenase and protein. Moreover, there was a significant increase in tumor markers and CRP in patients with mixed ascites versus patients with non-mixed ascites. Using logistic regression analysis, the predictor variables for mixed ascites in cirrhotic patients included positive tumor markers CEA and CA 19-9 and positive CRP. *Conclusion.* in our study, the commonest cause of mixed ascites was malignancy. Significant predictors of mixed ascites were CRP and tumor markers; CEA, CA 19-9 and CA 125.

Keywords: Mixed ascites, liver cirrhosis, and serum-ascites albumin gradient.

Introduction

Ascites is the pathologic accumulation of fluid in the abdominal cavity. It is a very common manifestation of decompensated liver cirrhosis[1,2]. Although many pathogenetic processes have been implicated in the development of ascites, about 75% likely occur as a result of portal hypertension in the setting of liver cirrhosis with the remainder due to infectious, inflammatory and infiltrative conditions[3]. Ambulatory patients with an episode of cirrhotic ascites have a 3-year mortality rate of 50%. However, development of refractory ascites carries a poor prognosis with a 1-year survival rate of less than 50%[4]. Although ascites has many etiologies, they can be classified according to serum-ascites albumin gradient (SAAG) into high SAAG (≥ 1.1 gm/dL) and low SAAG (<1.1 gm/dL). High SAAG indicates that the ascites is mainly due to sinusoidal hypertension and/or low ascitic fluid protein content as in cirrhosis, heart failure, constrictive pericarditis, kwashiorkor, myxedema and fatty liver of pregnancy. Low SAAG indicates the presence of ascites with high ascitic fluid protein content which develops when the peritoneum is involved by malignancy or tuberculosis due to leakage of high protein mesenteric lymph from obliterated lymphatics and inflamed peritoneum[5,6]. Etiologically, ascites may also be classified to result from either local or systemic pathologies[7]. Some forms of local ascites include malignant ascites, such as ovarian, endometrial, colorectal, gastric, pancreatic, peritoneal malignancies, lymphomas and ascites secondary to acute and chronic pancreatitis[8]. Other rare inflammatory causes include idiopathic sarcoidosis and systemic lupus erythematous[9,10]. Mixed ascites is defined in approx. 5% of patients in whom two or more etiologies of ascites are demonstrated. Such patients have liver cirrhosis plus (an) other local and/or systemic cause(s). Examples of mixed ascites include liver cirrhosis plus peritoneal carcinomatosis, peritoneal tuberculosis, heart failure or renal failure and liver cirrhosis plus heart failure and diabetic nephropathy. In the latter case, cirrhosis complicates non-alcoholic steatohepatitis[11].

Patients and Methods

This cross sectional study was carried out in Tropical Medicine Dept., Faculty of Medicine, Zagazig University Hospitals in the period from Sep. 2018 to June 2019. The study was conducted on 273 cirrhotic ascitic patients. The diagnosis of liver cirrhosis in all cases was established upon clinical, laboratory and radiologic investigations[12,13]. The diagnosis of ascites was established upon clinical and radiologic investigations. Non-cirrhotic ascitic patients were excluded from the study. Informed consents were obtained from all patients to participate in the study. The study was approved by the ethical committee of the Faculty of Medicine, Zagazig University. There were no conflicts of interest and no funding during the study. All patients were subjected to the following: **1)** Full history taking and thorough general and local

examinations. **2)** Laboratory investigations included complete blood count using an automated blood counter, liver and kidney function tests using calorimetric methods [serum albumin, serum bilirubin, ALT and AST, prothrombin time (PT), International Normalized Ratio (INR) and serum creatinine using the appropriate biochemical methods]. Alpha fetoprotein (AFP) (reference range 0-10 ng/mL), cancer antigen 19-9 (CA 19-9) (reference range 0-37 U/mL with cutoff value of 37 U/mL for diagnosis of pancreatic cancer[14]), carcinoembryonic antigen (CEA) (reference range 0-3 ng/mL with cutoff value of 3 ng/mL for diagnosis of gastrointestinal cancer[15]) and cancer antigen 125 (CA 125) (reference range 0-35 U/mL with cutoff value of 35 U/mL for diagnosis of ovarian cancer[16]) were assessed using the appropriate biochemical methods. **3)** Ascitic fluid investigations included cytologic and biochemical analyses, Ziehl-Neelsen staining of ascitic fluid and serum-ascites albumin gradient (SAAG). **4.** Radiologic investigations included pelvi-abdominal ultrasonography (real time machine with a transducer of 3.5 MHz (My Lab 20) was used), pelvi-abdominal triphasic CT (medical imaging systems generating three-dimensional images of internal body structures using complex x-ray and computer-aided tomographic imaging techniques. The CT scan machine used was Toshiba 4-slice manufactured by a Japanese company) and echocardiography (Siemens machine was used).

Statistical analyses

Statistical analyses were carried out using SPSS version 17.0 software (SPSS Inc., Chicago, Illinois, USA). Data were expressed as number and percentage for qualitative variables and mean ± standard deviation for quantitative ones. Student "t" test was used for comparison of means of two independent groups. Logistic regression analysis of predictor variables for mixed ascites in cirrhotic ascitic patients was performed. The P value is considered significant if < 0.05.

Results

Table 1 shows the clinical and laboratory data of the studied patients. **Figure 1** shows that, 28 patients (10.3%) among the studied patients were mixed ascites. **Table 2** shows that, among patients with mixed ascites, the most common cause is malignancy in 11 patients (39.2%) while cardiac causes were present in 7 patients (25%), renal causes were present in 2 patients (7.1%) and surgical causes were present in 8 patients (28.7%). Comparison between mixed and non-mixed ascitic patients as regard ascitic fluid analysis demonstrated that there was a statistically significant increase regarding total lecocytic count, lactate dehydogenease and ascitic fluid protein and significant decreased in SAAG, ascitic fluid glucose in patients with mixed ascites versus patients with non-mixed ascites. Ziehl-Neelsen staining of all ascitic samples yielded no tuberculous cases, **tab. (3)**. Comparison between mixed ascites and non-mixed ascites patients as regard tumor markers (CEA, CA125, CA19-9 and AFP) and CRP demonstrated that there was a significant increase in studied tumor markers and CRP in patients with mixed ascites versus patients without mixed ascites, **tab. (4)**. Logistic regression analysis of predictor variables for mixed ascites in cirrhotic ascitic patients showed that the predictor variables for mixed ascites in cirrhotic ascitic patients included positive tumor markers CEA and CA 19-9 and positive CRP, **tab. (5)**.

Table 1. The clinical and laboratory data of the studied patients (N=273).

Parameter	Mean ±SD
Male/female	138/135
Age (years)	58±10.7
WBC ($x10^3/mm^3$)	5.83±3.2
RBCs ($x10^6/mm^3$)	3.5±0.77
Hemoglobin (g/dL)	09.9±20
Platelets ($x10^3/mm^3$)	110±36.4
AST (U/L)	67.8±20.4
ALT (U/L)	39±12.10
Total bilirubin (mg/dL)	2.8± .85
Direct bilirubin (mg/dL)	1.7±.72
Albumin (g/dL)	2.4±0.63
Creatinine (mg/dL)	1±0.45
PT (seconds)	18±4.5
SAAG	1.5±0.40
Ascitic TLC	284±94.4
CRP (mg/mL)	21.15 ± 9.3
CEA (ng/mL)	34.2 ± 10. 75
CA125 (U/mL)	134.4 ± 32.6
CA19-9 (U/mL)	134.4 ± 32.6
AFP (ng/mL)	103 ± 36.50

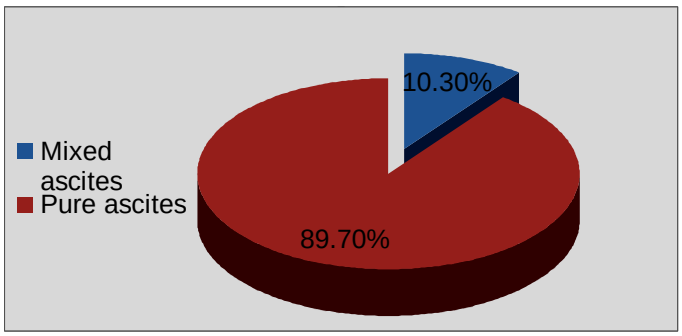

Figure 1. Percent of mixed ascites (28 patients) in studied patients

Table 2. Frequency distribution of causes of mixed ascites (N = 28) among the studied patients.

Causes of mixed ascites	Number (28)	%
Tumors		
- Ruptured hepatoma	4	14.3
- Lymphoma	2	7.1
- Cancer ovary	2	7.1
- Cancer pancreas	1	3.6
- Cancer colon	2	7.1
Cardiac disease	7	25
Renal disease	2	7.1
Surgical abdomen		
- Mesentric vascular occlusion	4	14.3
- Perforated viscous	2	7.1
- Perforated gall bladder	1	3.6
- Perforated appendix	1	3.6
Total	**28**	**100**

Table 3. Comparison between mixed and non-mixed ascitic patients as regard ascitic fluid analysis.

	Mixed ascites (N = 28) Mean M±SD	Non-mixed Ascites (N = 245) Mean ±SD	P
TLC/mm^3	347±116	276± 93.2	0.046
SAAG	1.4±0.4	1.56±0.4	0.005
Fluid Glucose mg/dl	101±33.7	136±45.54	0.002
Fluid LDH u/l	242±80.67	134±44.7	0. 0001
Fluid Protein g/dl	1.9±0.66	1.15±0.38	0.0001

Table 4. Comparison between mixed ascites and non-mixed ascites patients as regard tumor markers and CRP.

Tumour marker	No.	Mixed ascites (N = 28) No. (%)	Non mixed ascites (N = 245) No. (%)	P
CEA				
High	10	8 (80)	2 (20)	0.001
Normal	263	26 (9.9)	237 (90.1)	
CA125				
High	10	7 (70)	3 (30)	0.001
Normal	271	21 (8)	242 (92)	
CA19-9				
High	3	2 (67)	1 (33)	0.001
Normal	270	26 (10)	244 (90)	
AFP				
High	15	11 (63)	4 (27)	0.031
Normal	258	24 (9)	234 (91)	
CRP				
High	169	24(14)	145(86)	0.006
Normal	104	4(4)	100(96)	

Table 5. Logistic regression for predictor variables for mixed ascites in cirrhotic ascitic patients.

	Sig.	EXP (B)	95 % CI for EXP (B)	
			Lower	Upper
Age	0.6	0.99	0.934	1.04
CEA (high)	0.008	11.5	1.872	71
CA19-9 (high)	0.003	1.5	.063	35
CRP (high)	0.04	3.3	1.05	10.6
Sex (female)	0.054	2.6	0.982	6.8

EXP (B): exponentiation of coefficients; **CI**: confidence interval.

Discussion

The major complications of liver cirrhosis include ascites with spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding as a result of portal hypertension and HCC[3,17-22]. Mixed ascites is defined in approximately 5% of patients in whom two or more etiologies of ascites are demonstrated. Such patients have liver cirrhosis plus (an) other local and/or systemic cause(s). The importance of this paper is that it highlights the state of mixed ascites, which explains the atypicality of some cases of cirrhotic ascites (rapid accumulation, rapid development of tense state, primary refractoriness and rapid re-accumulation after diuretic or therapeutic paracentesis response). Reaching a cause-based diagnosis of ascites in such cases allows better cause-targetted treatment. In the present study, the frequency of mixed ascites was 10.3%. Causes of mixed ascites included malignant diseases (39.2% of cases), cardiac diseases (25% of cases), renal diseases (7.1% of cases) and surgical diseases (28.6% of cases). Tasneem et al, reported that approximately 5% of patients with cirrhotic ascites had mixed ascites demonstrated by 2 or more underlying causes of ascites formation. Such patients had cirrhosis plus local or systemic causes such as peritoneal carcinomatosis, peritoneal tuberculosis, heart failure or diabetic nephropathy[11]. On the other hand, Dubey and Dawane stated that, many diseases are complicated by ascites and stated that the commonest cause of ascites is portal hypertension secondary to liver cirrhosis. They stated also that in about 20% of cases, there was an extra-hepatic cause of ascites with normal liver structure and function and about 5% of cases had more than one cause of ascites (mixed) usually cirrhosis with tuberculosis, malignancy, cardiac or renal diseases. They stated that appropriate treatment depends upon proper diagnosis[23]. Discrepancy of figures between the present study and those of Tasneem et al and Dubey and Dawane is attributed to the fact that our prevalence of mixed ascites is calculated among a group of cirrhotic ascitic patients while prevalence of mixed ascites in the former studies was calculated among a group of cirrhotic and non-cirrhotic ascitic patients. In the present study, we found that the value of SAAG of mixed ascites patients was lower than that of cirrhotic non-mixed ascites patients. This finding is in agreement with previous studies that found a high SAAG in all patients with cirrhotic portal hypertension and a low SAAG in mixed ascites[24]. SAAG is known to be used to differentiate ascitic fluid into two categories; first high SAAG (≥ 1.1 g/dL) due to portal hypertension and low SAAG (< 1.1 g/dL) unrelated to portal hypertension. SAAG in mixed ascites patients is determined by which is predominantly of two opposing forces; the first which tends to raise SAAG in the form of portal hypertension and the second, which tends to reduce SAAG in the form of the local inflammatory or neoplastic process[25]. By comparing both groups of mixed and non-mixed ascites patients in the present study, the results showed a statistically significant increase as regard ascitic fluid analysis parameters (TLC, LDH and protein) in mixed ascites compared to non-mixed ascites. These results reflect the malignant and the surgical inflammatory nature of most cases of mixed ascites and are in agreement with Salerno et al, who reported similar results in malignant ascites[26]. In the present study, the results showed a statistically significant increase as regard, CRP in mixed ascites patients versus non-mixed ascites patients. These results reflect the malignant and the surgical inflammatory nature of most cases of mixed ascites and are in agreement with Wang and Sun who reported similar results in malignant ascites[27]. Also, by comparing both groups of mixed and non-mixed ascites patients in the present study, the results showed a statistically significant increase as regard tumor markers CEA, CA 125 and CA 19-9 in mixed ascites patients. Many studies demonstrated that patients with mixed ascites showed increased ascitic fluid tumor markers that reflect the malignant nature of most cases of mixed ascites[28-30]. Serum AFP was elevated in 4 out of 28 patients (14.3%) with mixed ascites; all of them were diagnosed as ruptured hepatoma proved by triphasic CT and diagnostic paracentesis. This result is in agreement with that of Letchumanan et al[31] who reported elevated AFP in 59% of patients with ruptured hepatoma and also in agreement with those of McHugh et al[32] who found a weak correlation between serum level of AFP and capsular invasion by HCC. On performing

logistic regression for predictor variables for mixed ascites in cirrhotic ascitic patients, it was found that significant predictor variables included positive tumor markers CEA and CA 19-9 and positive CRP. This finding reflects the malignant and the surgical inflammatory nature of most cases of mixed ascites and is an agreement with results of other studies about CEA, CA19-9 and CRP respectively in malignant ascites[27-29].

Conclusion

In our study, mixed ascites was diagnosed in approximately 10.3% of cirrhotic patients with ascites. The commonest cause of mixed ascites was malignancy in 39.2%.Significant predictors of mixed ascites were high CRP and tumor markers CEA and CA 19-9.

Abbreviations

AFP, Alpha fetoprotein; **CEA**, Carcinoembryonic antigen; **CA**, Cancer antigen; **SAAG**, Serum-Ascites Albumin Gradient; **CRP**, C-reactive protein

References

[1] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. **Gastroenterology**. 2007; 133 (2): 481-488.

[2] Pericleous M, Sarnowski A, Moore A, Fijten R, Zaman M. The clinical management of abdominal ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: a review of current guidelines and recommendations. **Eur J. Gastroenterol Hepatol**. 2016; 28 (3): e10-18.

[3] Elmoghazy M, El Shabrawi A, Mousa N. Portal hypertension, an overview**. Medical J. of Viral Hepatitis**. 2019; 4 (1): 15-21.

[4] Fede G, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, et al. Renal failure and cirrhosis: A systematic review of mortality and prognosis. **J. Hepatol**. 2012; 56 (4): 810-818.

[5] Rector W. An improved diagnostic approach to ascites (editorial). **Arch Intern Med**. 1987; 147: 215.

[6] Runyon B, Montano A, Akriviadis E, Antillon M, Irving M, McHutchison J. The serum-ascites albumin gradient is superior to the exudatetransudate concept in the differential diagnosis of ascites. **Annals of Internal Medicine**. 1992; 117 (3): 215-220.

[7] Carrier P, Jacques J, Debette M, Legros R, Sarabi M, et al. Non-cirrhotic ascites: Pathophysiology, diagnosis and etiology. **Société Nationalefrançaise de Médecine Interne**. 2013; 35 (6): 365-71.

[8] Smith E, Jayson G. The current and future management of malignant ascites. **Clin Oncol (R Coll Radiol.)** 2003; 15: 59-72.

[9] B'Chir Hamzaoui S, Abdallah M, Bouslama K, Mestiri H. Chylous ascites revealing a systemic lupus erythematosus. **Gastroenterologie Clinique et Biologique**. 2007; 31 (1): 100-10.

[10] Kaas R, Rustman L, Zoetmulder F. Chylous ascites after oncological abdominal surgery: Incidence and treatment. **European J. of Surgical Oncology**. 2001; 27 (2): 187-189.

[11] Tasneem H, Shahbaz H, Sherazi B. Pharmacoepidemiology of ascites and associated complications in hospitalized patients: Descriptive observational study. **Int. Current Pharmaceutical J**. 2015; 4 (2): 343-346.

[12] Schuppan D, Afdhal N. Liver cirrhosis. **Lancet**. 2008; 371: 838-851.

[13] Matsutani S, Fukuzawa T, Ebara M, Ohto M. Ultrasonography in the diagnosis of liver cirrhosis. **Nihon Rinsho**. 1994; 52 (1): 56-62.

[14] Goonetilleke K, Siriwardena A. Systematic review of cancer antigen 19-9 (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. **European J. of Surgical Oncology**. 2007; 33 (3): 266-270.

[15] Dong-Ze J, Ze Zhang, Hua-Guo X. Evaluation of serum CEA for the gastrointestinal cancer diagnosis using different cut-off values. **Int J Clin Exp Pathol**. 2016; 9 (8): 7807-7812.

[16] Shih M, Sokoll L, Chan D. Ovarian cancer. In: Diamandis E, Fritsche H, Lilja H, Chan D, Schwartz M. (eds.). **Tumor Markers: Physiology, pathobiology, technology and clinical application**s. AACC Press. Washington DC: 2002*:* 239-252.

[17] Park J, Chen M, Colombo M, Roberts L, Schwartz M, Chen J., et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: The BRIDGE Study. **Liver Int**. 2015; 35 (9): 2155-2166.

[18] Abdel-Razik A, Mousa N, Abdel-Aziz M, Elsherbiny W, Zakaria S, Shabana W. Mansoura simple scoring system for prediction of spontaneous bacterial peritonitis: lesson learnt. **Eur J. Gastroenterol Hepatol**. 2019; 31 (8): 1017-1024.

[19] Mousa N, Besheer T, Abdel-Razik A, Hamed M, Deiab A, Sheta T. Can combined blood neutrophil to lymphocyte ratio and C-reactive protein be used for diagnosis of spontaneous bacterial peritonitis?. **Br J Biomed Sci**. 2018; 75 (2): 71-75.

[20] Abdel-Razik A, Mousa N, Elbaz S, Eissa M, Elhelaly R, Eldars W. Diagnostic utility of interferon gamma-induced protein 10 kDa in spontaneous bacterial peritonitis: Single-center study. **Eur J. Gastroenterol Hepatol**. 2015; 27 (9): 1087-1093.

[21] Mousa N, Zakaria S, Abd EL Maksoud M, Shabana W, Effat N, Awad M. The Predictive Factors for Recurrence of Spontaneous Bacterial Peritonitis. **Medical J. of Viral Hepatitis**. 2018; 2 (2): pp. 25-29.

[22] Amr S, Abdel-Razik A, Hoda E. Spontaneous Bacterial Peritonitis: An Overview. **Medical J. of Viral Hepatitis**. 2018; 3 (1): pp. 13-17.

[23] Dubey T and Dawane S. Diagnostic value of serum ascites lipid gradients in patients with ascites. **Int. J. of Contemporary Medical Research**. 2016; 3: 2572-2577.

[24] Bindu C, Uday N. Clinical study of ascites with special reference to serum-ascites albumin gradient. **Int. J. of Medical Science and Public Health**. 2014; 3 (2): 169-72.

[25] Moore K, Aithal G. Guidelines on the management of ascites in cirrhosis. **Gut**. 2006; (Suppl 6): vi1-vi12.

[26] Salerno F, Restelli B, Incerti P, Annoni G, Capozza L, Badalamenti S, et al. Utility of ascitic fluid analysis in patients with malignancy-related ascites. **Scand J. Gastroenterol**. 1990; 25 (3): 251-6.

[27] Wang C, Sun C. C-reactive Protein and malignancy: Clinico-pathological association and therapeutic implication. **Chang Gung Med J**. 2009; 32: 471-82.

[28] Zuckerman E, Lanir A, Sabo E, Matter I, Yeshurun D, Eldar S et al. Cancer antigen 125: A sensitive marker of ascites in patients with liver cirrhosis. **Am J. Gastroenterol**. 1999; 94 (6): 1613-1618.

[29] Jung M, Jeung H, Lee S, Park J, Hong S, Noh SH, et al. The clinical significance of ascitic fluid CEA in advanced gastric cancer with ascites. **J. of Cancer Research and Clinical Oncology**. 2010; 136 (4): 517-526.

[30] Bhattarai A, Jha B, Timilsina S. Serum CA 19-9 levels in benign and malignant diseases associated with the gastrointestinal tract. **Annals of Clinical Chemistry and Laboratory Medicine**. 2015; 1 (2): 35-41.

[31] Letchumanan V, Lim K, Mohamad A. Diagnosis and management of ruptured hepatoma: single center experience over 10 years. **Med J. Malaysia**. 2013; 68 (5): 405-409.

[32] McHugh P, Gilbert J, Vera S, Koch A, Ranjan D, Gedaly R. Alpha-fetoprotein and tumour size are associated with microvascular invasion in explanted livers of patients undergoing transplantation with hepatocellular carcinoma. **HPB (Oxford)**. 2010; 12 (1): 56-61.